Proportion of Lifetime UV Dose Received by Age 18, What Stern *et al* Actually Said in 1986

To the Editor:

I read with interest Thieden *et al*'s (2004) study that assessed UV exposure among children, teenagers, and adults in Copenhagen. As have many "campaigns" and most of the more than 200 publications that cite our work that I have read, the authors appear to have failed to understand our findings and misquote our work (Stern *et al*, 1986).

We developed a mathematical model of the relation of UV exposure, age, and other factors to non-melanoma skin cancer (NMSC) risk. We used this model to estimate the risk reduction that could be achieved with the regular use of a high SPF sunscreen for NMSC. Our model predicted that consistent use of high SPF sunscreen to age 18 would reduce the lifetime risk of NMSC by 78% (base case analysis). In our base case analysis, we assumed that children living in the northern United States spend three times as much time in the sun as adults annually. This assumption is consistent with slightly less than half of the total lifetime sun exposure occurring by age 18.

Because we understood that our base case assumption about sun exposure was based on scant data and the ratio of childhood to adult sun exposure would affect the predicted effect of childhood sun protection on lifetime skin cancer risk reduction, our model included an independent variable to account for the variability in the ratio of annual child to adult sun exposure, which we termed the sun affinity ratio (SAR) (Table I) (Fig 1).

Our sensitivity analyses examined the impact of various assumptions about sun exposure patterns over a lifetime (i.e., varying SAR) on the primary endpoint: lifetime NMSC risk reduction with effective UV protection up to age 18. One full journal page of our paper as well as a figure and a table (*reproduced here from Stern, 1986*) detailed these concerns and the range of assumptions about sun exposure habits over a lifetime that we utilized in our sensitivity analysis. The extreme low and high assumptions of SAR that we utilized in our sensitivity analysis are consistent: 16% and 78% of total lifetime UV exposure occurring up to age 18, respectively. The extreme high case would describe a youthful sun worshiper who becomes a compulsive sun avoider after age 18.

The greater importance of sun exposure early in life than in adult years for NMSC lifetime risk, particularly basal cancer risk, is supported by epidemiologic studies performed subsequent to our study (Gallagher, 1995; Corona *et al*, 2001). Our model, which assumed a multistage model of carcinogenesis, accounted for the latency between exposure to a carcinogen and the actual development of the cancer. Such a latency period is observed for most cancers. As a result, the same UV exposure many years in the past (i.e., as a youth) is likely to have been a greater contributor to the development of a skin cancer that develops in an adult than a comparable quantity of recent exposure. Because of latency between exposure and cancer, when we assumed annual sun exposure is the same throughout life (SAR = 1% and 21% of lifetime exposure occurring to age 18), the reduction in lifetime skin cancer risk predicted with high levels of sun protection to age 18 decreased to 62% from our base case prediction of 78% risk reduction (with SAR = 3% and 45% of exposure occurring up to age 18).

Of course, the pattern of an individual's sun exposure over a lifetime is likely to be an even more complex one than described by the SAR. We are pleased that our early work has stimulated studies such as Thieden's, which attempts to quantify sun exposure patterns. But, an assessment of the robustness of Thieden's findings and their relevance to our base case assumptions should consider changes in habits over the last two decades as well as the generalizability and precision of Thieden's findings.

Since the 1980s, sun exposure habits may have changed. Perhaps the message that we and others subsequently emphasized, decreasing childhood sun exposure is particularly important for NMSC risk reduction, has actually reduced sun-seeking behavior in children more than adults (i.e., decreased the SAR).

Data from Denmark may not reflect US conditions. My lucky adult Scandinavian friends seem to have nearly as much opportunity for sun exposure as their children (SAR = 1) and along with my children have at least three times the summer vacation I have (i.e., SAR = 3). These differences from my small and admittedly biased sample highlight the cultural and social determinants of SAR and the importance of unbiased sampling if estimates that accurately reflect a large population too are achieved. Thieden's sample of Danish health care workers and golfers seems unlikely to be an ideal one to assess sun exposure patterns in the general population.

Thieden does not detail the power or precision of her estimates. But, the groups she studied are quite small (less than five subjects per year of age for those less than 20 and less than two subjects per year of age over age 20). Even if the authors were fortunate enough to have recruited a sam-

Table I. Sun affinity ratios (SAR) used in the analysis of skin cancer risk[a]

	Adult sun affinity		
Child sun affinity	Low[b]	Average	High[c]
Low[d]	6	2	2/3
Average	9	3	1
High[e]	12	4	$1\frac{1}{2}$

[a]An average child is assumed to have three times the annual sun exposure of an average adult.
[b]One-third times average.
[c]Three times average; nine times low.
[d]Two-thirds times average.
[e]One and one-third times average; two times below.
Reference: Stern (1986).

Abbreviations: NMSC, non-melanoma skin cancer; SAR, sun affinity ratio

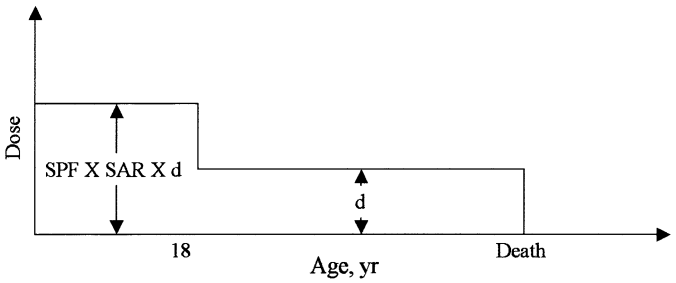

Figure 1
Age pattern of ultraviolet-B exposure. SPF indicates sun protective factor; SAR, sun affinity ratio; and d, dose affiliations

ple that is truly representative of the Danish population, Thieden's findings are likely to be more applicable to 21st-century Denmark, a quite northern country (latitude 55°) blessed with far more generous vacations than those who worked in not quite tropical Boston (latitude 42°) in the 1980s.

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References

Corona R, Dogliotti E, D'Errico M, *et al*: Risk factors for basal cell carcinoma in a Mediterranean population: Role of recreational sun exposure early in life. Arch Dermatol 137:1162–1168, 2001

Gallagher RP, Hill GB, Bajdik CD, Fincham S, Coldman AJ, McLean DI, Threlfall WJ: Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. Arch Dermatol 131: 157–163, 1995

Stern RS, Weinstein MC, Baker SG: Risk reduction for nonmelanoma skin cancer with childhood sunscreen use. Arch Dermatol 122:537–545, 1986

Thieden E, Philipsen PA, Sandby-Moeller J, Heydenreich J, Wulf HC: Proportion of lifetime UV dose received by children, teenagers and adults based on time-stamped personal dosimetry. J Invest Dermatol 123:1147–1150, 2004

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Vitamin D Induces the Antimicrobial Protein hCAP18 in Human Skin

To the Editor:

Cathelicidins are a class of mammalian antimicrobial peptides expressed in leukocytes and at epithelial surfaces (Zanetti, 2004). Human cathelicidin antimicrobial protein hCAP18 is encoded by *CAMP* (Ensembl Gene ID ENS G00000164047) on chromosomal location 3p21 and is the sole cathelicidin protein in humans. Recent studies have shown that cathelicidins, in addition to being antimicrobial, are multifunctional proteins with receptor-mediated effects on eukaryotic cells and activity in chemotaxis, angiogenesis, and wound healing (Zaiou *et al*, 2003; Zanetti, 2004). In the skin, there is low constitutive expression of hCAP18 in the basal layer of keratinocytes but rapid upregulation upon inflammation and injury (Frohm Nilsson *et al*, 1999; Dorschner *et al*, 2001; Heilborn *et al*, 2003).

Molecular mechanisms controlling the expression of *CAMP* are still poorly understood. We have investigated whether its expression could be influenced by agents that affect the proliferation and differentiation of skin keratinocytes. Human neonatal epidermal keratinocytes (Cascade Biologics, Portland, Oregon) were cultured in EpiLife serum-free keratinocyte growth medium (Cascade Biologics) containing growth supplements and a calcium concentration of 0.06 mM. At 60% confluency, the agents assayed were added to the medium and cells were harvested after 24 h. RNA was extracted and reverse transcribed by standard methods, and the expression was quantified by Real-Time RT-PCR on an ABI Prism 7700 (Applied Biosystems, Foster City, California) using 5 ng of cDNA according to standard protocols. Sequences were 5′-GTCACCAGAGGATTGTGACTTCAA-3′ and 5′-TTGAGGGTCACTGTCCCCATA-3′ for the primers, and 6-FAM–5′-CCGCTTCACCAGCCCGTCCTT-3′–BHQ1 for the fluorigenic probe.

An upregulation of *CAMP* of about one order of magnitude was achieved by treatment with 100 nM MC903/calcipotriol, a vitamin D analog applied for psoriasis treatment (Kragballe, 1995). Calcium is known to regulate major functions of the epidermis including terminal differentiation. Pretreatment of cells by 1.5 mM calcium for 48 h increased the expression by about 1.5-fold, and was synergistic to the effects of MC903 (Fig 1*a*). Based on these findings, we assayed the effect of vitamin D and its metabolites (all from Fluka, Buchs, Switzerland). Both biologically active forms of vitamin D_3, i.e., $1,25(OH)_2D_3$ and $25(OH)D_3$, stimulated *CAMP* expression at the same magnitude as MC903. The corresponding vitamin D_2 analogs were slightly less efficient. All compounds were active down to levels of 10 nM (shown for $1,25(OH)_2D_3$). The precursor of vitamin D biosynthesis, 7-dehydrocholesterol (7-DHC), was ineffective. Western blot analysis confirmed that the elevated transcription was reflected on the protein level (Fig 1*b*).

An *in silico* analysis revealed two putative vitamin D responsive elements (VDRE) of the DR3 type, and one putative heterodimer site of the DR5 type, within 1 kb upstream of the transcription start (Table I). This region was subcloned